PRODUCT INFORMATION – ETOPOSIDE (ETOPOSIDE)

1. NAME OF THE MEDICINE

Etoposide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Etoposide Injection is a sterile solution containing etoposide 20 mg/mL in an organic solvent base.

Excipient with known effect: Ethanol

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Concentrate for Solution for Infusion

Etoposide is a white or almost white, crystalline powder, practically insoluble in water, sparingly soluble in methanol, slightly soluble in alcohol and in methylene chloride.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Small cell carcinoma of the lung.
- Acute monocytic and myelomonocytic leukaemia.
- Hodgkin's disease.
- Non-Hodgkin's lymphoma.

4.2 Dose and method of administration

Dosage

The usual dose of etoposide must be based on the clinical and haematological response and tolerance of the patient. A repeat course of etoposide should not be administered until the patient's haematological function is within acceptable limits (see section 4.4 Special warnings and precautions for use).

Adult

The dosage for Etoposide Injection is 50-60 mg/m^2/day intravenously for 5 consecutive days followed by a treatment free interval of 2-3 weeks. Total dose should not usually exceed 400 mg/m^2 per course. In any case, repeat courses should

not be given until the haematological parameters have been checked for evidence of myelosuppression and found to be satisfactory.

Method of administration

Plastic devices made of acrylic or ABS (a polymer of acrylonitrile, butadiene and styrene) have been reported to crack or leak when used with undiluted Etoposide injection.

Etoposide should only be given by slow intravenous infusion (see section 4.4 Special warnings and precautions for use, section 4.8 Adverse effects (undesirable effects)).

Etoposide should not be administered by intrapleural or intraperitoneal injection.

Etoposide must be diluted before administration. Resultant concentrations should not be greater than 0.4 mg/mL since precipitation can occur. Usually etoposide is added to 250 mL of 0.9% sodium chloride or 5% glucose. The infusion should be administered over a period of 30-60 minutes.

Contact with buffered aqueous solutions with pH above 8 should be avoided. Concentrations of etoposide of 0.4 mg/mL in 5% glucose or 0.9% sodium chloride are **chemically** stable for 24 hours when stored at room temperature. However, to reduce microbiological hazard, admixtured solutions should be used as soon as practicable after preparation. If storage is required hold at 2-8°C for no more than 24 hours. Contains no antimicrobial preservative, use once only and discard any residue.

The use of a Pharmacy Bulk Pack should be restricted to suitably qualified pharmacists operating in suitably equipped hospital pharmacies or compounding centres. The Pharmacy Bulk Pack is intended for multiple dispensing into sterile solutions for subsequent infusion in individual patients in one treatment session. The Pharmacy Bulk Pack should be spiked only once.

Dosage Adjustment

Hepatic impairment

Etoposide is contraindicated in severe hepatic dysfunction, and it should be used with caution in patients with mild to moderate hepatic impairment.

Renal impairment

Since some etoposide (approximately 30%) is excreted unchanged in the urine, dosage adjustment may be needed in patients with impaired renal function.

4.3 Contraindications

- Severe hepatic dysfunction.
- Hypersensitivity to any of the injection ingredients.
- Severe bone marrow failure (WBC less than 2.0 x 10^9/L or platelet count less than 75.0 x 10^9/L) not due to malignant disease.

- Acute infections.
- Pregnancy.
- Lactation.

4.4 Special warnings and precautions for use

Etoposide should be administered only under constant supervision by physicians experienced in therapy with cytotoxic agents and only when potential benefits of etoposide therapy outweigh the possible risks. Appropriate facilities should be available for adequate management of complications should the need arise.

Myelosuppression

Cytotoxic agents, including etoposide, may produce myelosuppression (including, but not limited to, leukopenia, granulocytopenia, pancytopenia and thrombocytopenia).

Haematological function must be frequently and carefully monitored during and after etoposide therapy. Complete blood counts (leucocyte count with differential, platelet count, haemoglobin) should be performed prior to initiation of etoposide therapy and before each subsequent course of treatment with the drug. The occurrence of a platelet count below 50.0 x 10^9/L indicates that the patient is at risk of bleeding; the occurrence of a total white cell count below 3.0 x 10^9/L or an absolute neutrophil count below 0.5 x 10^9/L indicates that the patient is at risk of infection. Therapy should not be commenced if there is a risk of the platelet count, the white cell count, or the neutrophil count falling below these levels. If the counts drop below these levels during therapy, further therapy should be withheld until the blood counts have sufficiently recovered (platelets above 100 x 10^9/L, leucocytes above 4.0 x 10^9/L), this is usually within 10 days.

Clinical consequences of severe myelosuppression include infections. Viral, bacterial, fungal and/or parasitic infections, either localised or systemic, may be associated with the use of etoposide alone or in combination with other immunosuppressive agents. These infections may be mild, but can be severe and at times fatal.

Infections must be brought under control prior to initiating etoposide therapy. Bone marrow suppression may increase the risk of septicaemia. Combined chemotherapy may increase bone marrow suppression and should be used with caution. If radiotherapy and/or chemotherapy are used prior to etoposide, an adequate interval, enabling bone marrow recovery should be allowed.

Anaphylactoid reactions

Physicians should be aware of the possibility of anaphylactoid reactions manifesting as chills, fever, bronchospasm, tachycardia, dyspnoea and hypotension (see section 4.8 Adverse effects (undesirable effects)). Hypotensive reactions can be reduced by prolonging the infusion period. Anaphylactic responses have usually responded to cessation of therapy and administration of pressor agents, corticosteroids, antihistamines or volume expanders, as appropriate.

Myocardial infarction

Myocardial infarction has been observed in patients treated with etoposide as part of multi-agent chemotherapy. Patients with prior history of mediastinal radiation or recipients of previous chemotherapies may be at risk (see section 4.8 Adverse effects (undesirable effects)).

Secondary leukaemia

The occurrence of acute leukaemia, which can occur with or without a preleukaemic phase has been reported rarely in patients treated with etoposide in association with other antineoplastic drugs.

Neither the cumulative risk, nor the predisposing factors related to the development of secondary leukaemia are known. The roles of both administration schedules and cumulative doses of etoposide have been suggested, but have not been clearly defined.

Tumor lysis syndrome (TLS)

Tumor lysis syndrome, sometimes fatal, has been reported following the use of etoposide in association with other chemotherapeutic drugs. Patients at high risk of TLS such as patients with high proliferative rate, high tumor burden, and high sensitivity to cytotoxic agents should be monitored closely and appropriate precaution should be taken (see section 4.8 Adverse effects (undesirable effects)).

Immunosuppressant effects/Increased susceptibility to infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents, including etoposide, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving etoposide. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Toxicity

Etoposide has a low therapeutic index, and a therapeutic response is not likely to occur without evidence of toxicity.

Administration

Etoposide Injection is for administration by intravenous infusion only and is not to be administered by other routes.

Etoposide should be given only by slow intravenous infusion (usually over a 30-60 minute period), since hypotension has been reported as a possible side effect of rapid intravenous infusion.

Extravasation

Care should be taken to avoid extravasation during infusion as the drug is irritating to surrounding tissues. Soft tissue inflammation and irritation may occur, but ulceration is generally not seen following extravasation with dilute solution. If leakage occurs, the injection should be discontinued immediately and any remaining portion of the dose should be introduced into another vein. Usual extravasation procedures should be followed.

Hyperuricaemia

Hyperuricaemia has been reported following the first course of treatment with etoposide.

Contraception

Etoposide should not normally be administered to patients who are pregnant (see section 4.6 Fertility, pregnancy and lactation, Use in Pregnancy) as safe use has not been established. Animal studies have shown etoposide to be teratogenic and embryocidal. Women of childbearing potential should be advised to avoid becoming pregnant whilst receiving etoposide therapy.

Other

Etoposide injection also contains ethanol as an excipient: this may be a risk factor in patients suffering from liver disease, alcoholism, epilepsy, children and in pregnant women.

Use in hepatic impairment

Etoposide has been shown to reach high concentrations in the liver, thus presenting a potential for accumulation in cases of functional impairment. Patients with impaired hepatic function may develop more profound myelotoxicity during treatment with etoposide. Transient elevations in liver enzymes and bilirubin may occur. Severe hepatic dysfunction is a contraindication to etoposide treatment, and mild to moderate impairment requires careful monitoring.

Use in renal impairment

Etoposide has been shown to reach high concentrations in the kidney, thus presenting a potential for accumulation in cases of functional impairment. Since a substantial fraction of etoposide is excreted unchanged in urine (approximately 30% of an intravenous dose), adjustment may be necessary in patients with impaired renal function. Monitoring during and following therapy is recommended.

Use in the elderly

As for adults, caution may be necessary in renal or hepatic impairment.

Paediatric use

Safety and effectiveness in children have not been established. Polysorbate 80 (contained as a solvent diluent) has been associated with severe adverse reactions in premature infants.

Effects on laboratory tests

Periodic complete blood counts, hepatic and renal function tests and serum urate, should be performed during treatment with etoposide. These tests should be performed prior to therapy and at appropriate periods during a course of treatment.

4.5 Interactions with other medicines and other forms of interactions

Etoposide Injection should not be physically mixed with any other drug. Parenteral drugs should be inspected for particulate matter and discolouration prior to use.

High-dose cyclosporine, resulting in plasma concentrations above 2,000 ng/mL, administered with oral etoposide has led to an 80% increase in etoposide exposure (AUC) with a 38% decrease in total body clearance of etoposide compared to etoposide alone.

Concomitant cisplatin therapy is associated with reduced total body clearance of etoposide.

Concomitant phenytoin therapy is associated with increased etoposide clearance and reduced efficacy, and other enzyme-inducing antiepileptic therapy may be associated with increased etoposide clearance and reduced efficacy.

Co-administration of warfarin and etoposide may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended.

Cross-resistance between anthracyclines and etoposide has been reported in preclinical experiments.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Etoposide may decrease male fertility.

Use in pregnancy – Pregnancy Category D

Etoposide may cause foetal harm when administered to pregnant women. Etoposide has been shown to be teratogenic and embryotoxic in mice and rats and its use in pregnant women is not recommended. Etoposide should only be used in women of child-bearing potential if the expected benefits outweigh the risks of therapy and adequate contraception is used. If the patient becomes pregnant whilst receiving the drug she should be advised of the potential hazard to the foetus.

Males undergoing treatment with etoposide should employ contraceptive measures (see section 5.3 Preclinical safety data).

Use in lactation

It is not known whether etoposide is excreted in breast milk so breast feeding should be discontinued during ETOPOSIDE therapy in lactating women.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Bone marrow suppression is the most likely life threatening effect. Cardiotoxicity has been reported.

More Common	
Blood and lymphatic system disorders	**Myelosuppression:** Haematological toxicity is the major and dose limiting adverse effect. It manifests mainly as leukopenia (principally granulocytopenia). The granulocyte count nadir occurs 7-14 days after treatment, and recovery is usually by days 20-22. Thrombocytopenia occurs less frequently. Anaemia may occur. Myelosuppression is not cumulative, but may be more severe in patients previously treated with other antineoplastic agents or radiotherapy (see section 4.4 Special warnings and precautions for use).
Gastrointestinal disorders	Nausea and vomiting frequently occur and may be treated symptomatically. Other adverse effects include abdominal pain, anorexia, oesophagitis and diarrhoea. Stomatitis has been reported in 1-6% of patients.
Skin and subcutaneous tissue disorders	**Alopecia:** Reversible alopecia, sometimes progressing to total baldness, has been observed in up to 66% of patients. The degree of alopecia is dose related.
Vascular disorders	**Hypotension:** Following rapid intravenous administration hypotension may occur. To avoid this, etoposide should be given by infusion over at least 30 minutes.
Less Common	
Immune system disorders	**Allergic Reactions:** Anaphylactic-like reactions characterised by chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension have been reported. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate (see

	section 4.4 Special warnings and precautions for use). Higher rates of anaphylactoid reactions have been reported in children who received infusions of concentrations higher than those recommended.
Cardiac disorders	Myocardial infarction, heart failure and life threatening cardiotoxicity have been reported.
Vascular disorders	**Local Effects:** Phlebitis has occurred following intravenous administration of etoposide, more usually with concentrated solutions. Hypertension and flushing have also been reported, however, blood pressure usually returns to normal a few hours after cessation of the infusion.
Nervous system disorders	**Neuropathy:** Peripheral neuropathy has occurred in a small percentage of patients receiving etoposide. Although not clearly established, it has been suggested that the risk and/or severity of peripheral neuropathy may be increased when etoposide is administered concurrently with other potentially neurotoxic agents (e.g. vincristine).
Respiratory, Thoracic and mediastinal disorders	Sudden fatal acute reactions associated with bronchospasm have been reported.
Rare	
Hepatobiliary disorders	Liver toxicity (elevations in serum bilirubin, AST and alkaline phosphatase concentrations). These effects were transient and resolved without sequelae.
Renal and urinary disorders	Renal toxicity (elevated urea levels and hyperuricaemia have been reported).
Infections and infestations	Septicaemia during high dose regimens.
Gastrointestinal disorders	Dysphagia.
Eye disorders	Transient cortical blindness.
Injury, poisoning, and procedural complications	Radiation recall dermatitis/phenomena.
Frequency not reported	
Infections and Infestations	Septic shock, sepsis, neutropenic sepsis, pneumonia, infection.
Nervous system disorders	Somnolence, aftertaste and seizures have been reported.
Respiratory, Thoracic and mediastinal disorders	Apnoea with spontaneous resumption of breathing following discontinuation has been reported.
Skin and subcutaneous	Rash, pigmentation disorder, pruritis, urticaria.

tissue disorders	
Cardiac disorders	Myocardial infarction, has been reported in patients treated with etoposide as part of multi-agent chemotherapy.
General disorders and administration site conditions	Fatigue, pyrexia and asthenia have been reported.
Metabolism and nutrition disorders	Tumor lysis syndrome, sometimes fatal, has been reported following the use of etoposide in association with other chemotherapeutic drugs.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

4.9 Overdose

No information is available relating to etoposide poisoning in humans. Haematological and gastrointestinal toxic effects are expected to be the principle manifestations of etoposide overdosage. Treatment will be mainly supportive. There is no known antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class: Antineoplastic agent. Etoposide is a semi-synthetic podophyllotoxin derivative.

Mechanism of action

The exact mechanism of action of etoposide is not known, however, it appears to produce cytotoxic effects by damaging DNA, thereby inhibiting or altering DNA synthesis. Etoposide is cell-cycle dependent, and cycle-phase specific, inducing G2-phase arrest and preferentially killing cells in the G2 and late S phases. Two different dose dependent responses have been observed. High concentrations (10 microgram/mL or more) cause cell lysis in cells entering mitosis. Low concentrations (0.3 to 10 microgram/mL) inhibit cells from entering prophase. Etoposide-induced DNA damage appears to correlate well with the cytotoxicity of the drug. Etoposide appears to induce single-stranded DNA breaks indirectly.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Following intravenous administration, peak plasma concentrations and plasma concentration versus time curves (AUC) exhibit marked inter-individual variation.

Distribution

Distribution of etoposide into human body tissues and fluids has not been fully characterised. Etoposide administered intravenously undergoes rapid distribution. Apparent steady-state volume of distribution averages 20-28% of bodyweight, or 18-29 L or 7-17 L/m^2 in adults and 5-10 L/m^2 in children. After intravenous administration etoposide is distributed minimally into pleural fluid, and has been detected in the saliva, liver, spleen, kidney, myometrium, healthy brain tissue and brain tumour tissue. Studies suggest distribution into bile is minimal. It is not known if etoposide is distributed into breast milk. Studies have shown etoposide crosses the placenta in animals. Etoposide penetrates the central nervous system (CNS) poorly, with cerebrospinal fluid (CSF) etoposide concentrations ranging from undetectable to less than 5% of concurrent plasma concentrations.

Limited data suggests etoposide distributes into brain tumour tissue more readily than into healthy brain tissue. Etoposide concentrations have been shown to be higher in healthy lung tissue than in lung metastases, but those achieved in primary myometrial tumours are similar to those achieved in healthy myometrial tissues. *In vitro*, etoposide is approximately 94% bound to serum proteins at a concentration of 10 microgram/mL.

Metabolism

In vitro studies suggest that metabolic activation of etoposide by oxidation into the O-quinone derivative might play an essential role in its activity against DNA. Etoposide is approximately 66% metabolised.

Excretion

Following intravenous administration, plasma concentrations of etoposide have generally been reported to decline in a biphasic manner, however, some data indicate the drug may exhibit triphasic elimination with a prolonged terminal phase. In adults with normal renal and hepatic function, the half-life of etoposide averages 0.6-2 hours in the initial phase and 5.3-10.8 hours in the terminal phase. In children with normal renal and hepatic function the half-life averages 0.6-1.4 hours in the initial phase and 3-5.8 hours in the terminal phase. After 72 hours, 44% of the administered dose was recovered in the urine, 29% as unchanged drug and 15% as metabolite. Recovery in the faeces ranged from less than 2% to 16% over three days. Total plasma clearance of etoposide has been reported as averaging 19-28 mL/minute/m^2 in adults and 18-39 mL/minute/m^2 in children with normal renal and hepatic function. Renal clearance approximates 30-40% of total plasma clearance. Dosage adjustment may be necessary in patients with impaired renal or hepatic function.

5.3 Preclinical safety data

Genotoxicity

Given its mutagenic potential, the drug could induce chromosomal damage in human spermatozoa; therefore males undergoing treatment with etoposide should employ contraceptive measures.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 300,

Polysorbate 80,

Citric acid,

Ethanol

6.2 Incompatibilities

Etoposide Injection should not be physically mixed with any other drug. Parenteral drugs should be inspected for particulate matter and discolouration prior to use. Plastic devices made of acrylic or ABS (a polymer of acrylonitrile, butadiene and styrene) have been reported to crack or leak when used with undiluted Etoposide Injection.

6.3 Shelf life

Refer to outer carton for expiration date.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

To reduce microbiological hazard, admixtures should be used as soon as practicable after preparation. If storage is necessary, hold at 2-8°C for no longer than 24 hours. Discard unused portion.

6.5 Nature and contents of container

Etoposide Injection 100 mg in 5 mL (sterile) Plastic Vial. (single pack)

Etoposide Injection 100 mg in 5 mL (sterile) Plastic Vial. (10’s pack)

Etoposide Injection 20 mg/mL in 25 mL (sterile) Plastic Vial. Pharmacy Bulk Pack, for hospital use only.

Etoposide Injection 20 mg/mL in 50 mL (sterile) Plastic Vial. Pharmacy Bulk Pack, for hospital use only.

Not all presentations may be available locally.

6.6 Special precautions for disposal

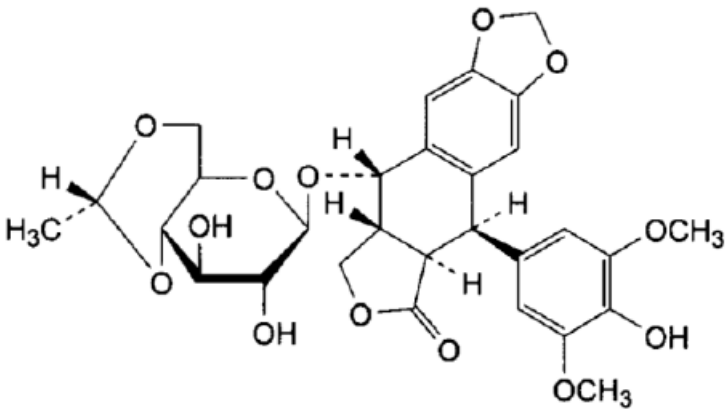
As with all antineoplastic agents, trained personnel should prepare Etoposide Injection. Reconstitution should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). The work surface should be protected by disposable, plastic-backed, absorbent paper. Protective gown, mask, gloves and appropriate eye protection should be worn when handling etoposide. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water and medical attention should be sought. It is recommended that pregnant personnel not handle cytotoxic agents such as etoposide. Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation. Items used to prepare Etoposide Injection, or articles associated with body waste, should be disposed of by placing in a double sealed polythene bag and incinerating at 1100°C.

Spills and disposal

If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with absorbent material such as absorbent towel of adsorbent granules. Collect up absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled ‘CYTOTOXIC WASTE FOR INCINERATION AT 1100°C’. Waste material should be incinerated at 1100°C for at least 1 second. Cleanse the remaining spill area with copious amounts of water.

6.7 Physicochemical properties

Chemical structure



Chemical name: 4'-demethylepipodophyllotoxin 9-[4,6-0-(R)-ethylidene-ß-D-glucopyranoside]

The empirical formula of etoposide is $C_{29}H_{32}O_{13}$.

CAS number: 33419-42-0

7. PRODUCT OWNER

Pfizer Inc.
235 East 42nd Street
New York 10017, USA

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